REMARKS/ARGUMENTS

I. Status of claims

Claim 1 is amended.

Claims 5-9 are withdrawn as they refer to non-elected species. Applicants reserve the right to rejoin these claims if the elected species are found to be allowable.

Claims 1-4 and 10-57 are pending.

Applicants thank the Examiner for agreeing to examine claims from restrictions Groups I and II.

II. Claims 1-4 and 10-13 satisfy 35 U.S.C. §101 requirements.

Claims 1-4 and 10-13 refer to "cell line". The terms "cell line", by itself, as understood in the art relate to an established cell culture that proliferates in a suitable medium *in vitro* and is not found in nature. Therefore, the claimed compositions are not found in nature as such and the terms "cell line" do not read on naturally occurring materials. Nevertheless, for the sake of expedited prosecution, applicants amend claim 1 to include the term "isolated". Therefore, applicants request the examiner to withdraw this rejection.

III. Claims 1-4 and 10-57 satisfy 35 U.S.C. §112 first paragraph enablement requirement.

The Examiner on page 3 of the Office Action rejected claims 1-4 and 10-57 for lack of enablement because the Examiner believes that it would require undue experimentation to practice the claims. The examiner has failed to establish a prima facie case of lack of enablement because the examiner has not shown why a skilled artisan would not be able to obtain a human cell line, that lacks major histocompatibility class I (MHC-I) antigens and major histocompatibility class II (MHC-II) antigens and which has been modified to express (i) a gene encoding an immunomodulator and (ii) a gene encoding an antigen of Epstein-Barr virus (EBV).

The instant application, in some embodiments, provides compositions and methods relating to human cell lines that lacks major histocompatibility class I (MHC-I) antigens and major histocompatibility class II (MHC-II) antigens and which have been modified to express an immunomodulator and an antigen of Epstein-Barr virus (EBV). Also provided by the present disclosure are methods of inducing or stimulating an immune response in a human to an EBV-associated cancer by administering one of the aforementioned compositions in an amount sufficient to induce or stimulate an immune response to the antigen of EBV expressed by the human cell line, whereupon an immune response to the EBV-associated cancer is induced. Thus, use of a bystander

line, e.g., K562 obviates the need for *in vitro* passaging or modification, such as by transduction, of each patient's tumor cells, thereby guaranteeing a constant amount of cytokine production without any intra- or inter-patient variability, while utilizing the patient-specific antigenic repertoire.

> In order to make a rejection, the examiner has the **initial burden to establish a reasonable basis to question the enablement** provided for the claimed invention. *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993) (examiner must provide a reasonable explanation as to why the scope of protection provided by a claim is not adequately enabled by the disclosure). MPEP 2164.04. (*emphasis added*).

The Examiner did not provide any evidence to show that generating a human cell line lacking MHC class I and class II antigens is not possible to practice the invention. To the contrary, the specification provides an exemplary cell line (K562) and on paragraph [0018], the application describes methods to generate human cell lines that are deficient in expressing MHC class I and II antigens on cell surface. The specification also mentions SK-MEL-33 as a suitable cell line (paragraph [0017] of the specification). In addition, the specification describes interfering with the expression and/or transport of α-chain of MHC class I antigens and α-β chains of MHC class II antigens. The specification also provides examples to generate suitable cell lines by providing dominant negative forms of the respective antigens and by transfection, retroviral infection or homologous recombination to achieve expression of modified MHC or β_2 microglobulin genes or inactivation of genes.

The test [for undue experimentation] is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the claimed invention. *Johns Hopkins Univ. v. Cellpro, Inc.*, 152 F.3d 1342, 1360 (Fed. Cir. 1998)(citing *PPG Indus., Inc. v. Gardian Indus. Corp.*, 75 F.3d 1158, 1564, 37 USPQ2d (BNA) 1618, 1623 (Fed. Cir. 1996)). The MPEP further states that the fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. *In re Certain Limited-Charge Cell Culture Microcarriers*, 221 USPQ 1165, 1174 (Int'l Trade Comm"n 1983), *aff'd. sub nom., Massachusetts Institute of Technology v. A.B. Fortia*, 774 F.2d 1104, 227 USPQ 428 (Fed. Cir. 1985). *See also In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404. The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. *In re Angstadt*, 537 F.2d 498, 504, 190 USPQ 214, 219 (CCPA 1976).

The K562 cell line is available as ATCC cell line CCL-243 as stated in the specification on paragraph [0017]. The specification further provides vector maps, sequences, and methods to obtain the claim modified cell lines, thereby obviating the necessity for biological deposits.

Therefore, the specification provides adequate disclosure and guidance to enable a skilled artisan to practice the pending claims. Applicants request the Examiner to withdraw the §112 rejections for claims 1-4 and 10-57.

IV. Claims 16-57 satisfy 35 U.S.C. §112 first paragraph enablement requirement.

On pages 5-6 of the Office Action, the Examiner rejected claims 16-57 for lack of enablement because the Examiner believes that "there is no sufficient evidence to support the broad scope of the scope [*sic*] of the claimed invention".

Pending claims 16-57 relate to methods of inducing or stimulating an immune response in a human to an EBV-associated cancer. The specification discloses EBV antigen-specific, GM-CSF-secreting cellular vaccine for treating EBV+ tumors in Example 2.

The Examiner cites to Draneff et al., (2002) and Nedospasov et al., (2007) in an attempt to show "[t]he state of art teaches that not all cytokine or immune modulators are benefit [*sic*] for the cancer treatment" and "whether his immunotherapeutic methods will be able to supersede other modern cancer treatment methods". (pages 5-6 of the Office Action).

None of the cited references cast doubt on the claimed methods to induce or stimulate immune responses in a human to an EBV-associated cancer. The Examiner cites to a passage in Nedospasov et al. that while acknowledging the efficacy of modern treatments, opines on the reproducibility of clinical effects:

> Numerous studies performed using sophisticated methods have convincingly demonstrated the possibility of induction of "correct" antigen-specific cytolytic T lymphocytes and their infiltration to the tumor… Unfortunately, **no clear reproducible clinical effects** were observed in these studies. (p. 324, left column). (*emphasis added*).

The examiner has not provided any specific evidence to show that the claimed methods would not work, but merely offers a general statement on cancer immunotherapy options and the reproducibility among its various treatment options. According to *In re Bowen*, 492 F.2d 859, 862-63, 181 USPQ 48, 51 (CCPA 1974), the minimal requirement is for the examiner to give reasons for the uncertainty of the enablement. MPEP 2164.04.

The examiner has not shown that administering a sufficient amount of a human cell line that is deficient in major histocompatibility class I (MHC-I) antigens and major histocompatibility class

II (MHC-II) antigens and which has been modified to express a gene encoding an immunomodulator and a gene encoding an antigen of Epstein-Barr virus (EBV) will not induce or stimulate an immune response to an EBV-associated cancer as in pending claims 16-57. None of the cited references suggest that the pending methods would not work or are unpredictable. The examiner further quotes from Nedospasov:

> It should also be mentioned that although adoptive transfer of T cells after ex vivo manipulations proved to be applicable for tumor treatment, it will hardly be **accessible for the majority of patients**, even developed countries. Therefore, one cannot predict, now, whether this immunotherapeutic method will be able to **supersede other modern cancer treatment methods**. (page 6, Office Action). (*emphasis added*).

While the pending claims 16-57 do not relate to adoptive transfer of T-cells, the Examiner's reliance on Nedospasov's views on patient accessibility and superseding other cancer treatment methods to show unpredictability is not a proper basis to reject the pending claims for lack of enablement. Despite the Examiner's acknowledgement that the level of the skill in the art of cancer treatment is "very high" (page 6, Office Action), the Examiner has not shown why a skilled artisan would be unable to practice the pending claims without undue experimentation.

Therefore, in summary, the Examiner has failed to show that the pending claims are not enabled. Nevertheless, as discussed herein, the specification as filed adequately enables the full scope of claims 16-57.

Applicants request the Examiner to withdraw §101 and §112 rejections and allow the pending claims. If an interview would help resolve the remaining issues, the Examiner is welcome to contact the applicants' representative.

No fees are due. However, please charge any fees that might be due in connection with this submission to our Deposit Account No. 12-0913 with respect to our matter number 43369-103949.

Respectfully submitted,

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